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Ritter, M ; Hess, O M ; Murakami, T ; Jenni, R ; Egloff, L ; Nonogi, H ; Schneider, J ; Krayenbuehl, H P

Abstract: In seven patients with aortic valve disease the time course of an auxotonic beat was compared with that of an isovolumetric beat produced by aortic cross clamping during open heart surgery. The rate of systolic stress rise (dS/dt; g · cm−2) of the isovolumetric beat at peak meridional wall stress (Sp; g · cm−2) of the auxotonic beat was determined by tipmanometry and simultaneous sonomicrometry and was found to be 87% of maximum dS/dt. In the second part of the study the stiffness index (k) was calculated in patients undergoing cardiac catheterisation according to: k = 0.87 · (max · dS/dt)/Sp · Vcf, where Vcf = normalised midwall circumferential fibre shortening velocity (circ · s−1). In 22 patients, 10 controls and 12 patients with aortic stenosis before (pre) and after (post) valve replacement the systolic stiffness index k (circ−1) was determined using tipmanometry and frame by frame angiocardiography. Muscle fibre diameter and interstitial fibrosis were assessed from left ventricular endomyocardial biopsies. The systolic stiffness index k was 15 circ−1 in controls, 14 in preoperative patients with aortic stenosis and 12 ($p<0.01$ v controls) in postoperative patients. There was a significant correlation between k and muscle fibre diameter ($r = 0.55$; $p<0.01$) but not between k and interstitial fibrosis or ejection fraction. We conclude that systolic stiffness index k is normal despite marked left ventricular hypertrophy in preoperative patients with aortic stenosis. Following successful valve replacement systolic stiffness index decreased and was significantly lower than in controls. Series elasticity appears to be determined by structures related to the muscle cell rather than to interstitial fibrosis

DOI: https://doi.org/10.1093/cvr/22.11.759

Cardiovascular Research, 1988, **22**, 759–767

Left ventricular systolic series elastic properties in aortic stenosis before and after valve replacement

MANFRED RITTER, OTTO M HESS, TOMOYUKI MURAKAMI, ROLF JENNI, LOUIS EGLOFF,† HIROSHI NONOGI, JAKOB SCHNEIDER,* HANS P KRAYENBUEHL

*From the Medical Policlinic, Cardiology; †Clinic of Cardiovascular Surgery; and *Institute of Pathology, University Hospital, Zurich, Switzerland*

ABSTRACT In seven patients with aortic valve disease the time course of an auxotonic beat was compared with that of an isovolumetric beat produced by aortic cross clamping during open heart surgery. The rate of systolic stress rise (dS/dt; $g \cdot cm^{-2}$) of the isovolumetric beat at peak meridional wall stress (S_p; $g \cdot cm^{-2}$) of the auxotonic beat was determined by tipmanometry and simultaneous sonomicrometry and was found to be 87% of maximum dS/dt. In the second part of the study the stiffness index (k) was calculated in patients undergoing cardiac catheterisation according to: $k = 0.87 \cdot (max \cdot dS/dt)/Sp \cdot Vcf$, where Vcf = normalised midwall circumferential fibre shortening velocity ($circ \cdot s^{-1}$). In 22 patients, 10 controls and 12 patients with aortic stenosis before (pre) and after (post) valve replacement the systolic stiffness index k ($circ^{-1}$) was determined using tipmanometry and frame by frame angiocardiography. Muscle fibre diameter and interstitial fibrosis were assessed from left ventricular endomyocardial biopsies. The systolic stiffness index k was 15 $circ^{-1}$ in controls, 14 in preoperative patients with aortic stenosis and 12 ($p<0.01$ *v* controls) in postoperative patients. There was a significant correlation between k and muscle fibre diameter ($r = 0.55$; $p<0.01$) but not between k and interstitial fibrosis or ejection fraction. We conclude that systolic stiffness index k is normal despite marked left ventricular hypertrophy in preoperative patients with aortic stenosis. Following successful valve replacement systolic stiffness index decreased and was significantly lower than in controls. Series elasticity appears to be determined by structures related to the muscle cell rather than to interstitial fibrosis.

Assessment of left ventricular function has focused on the behaviour of the ventricle as a pump (ejection phase indices) or as a muscle (isovolumetric contractile indices). Several models have been used to describe the contractile function of the heart muscle, not only in the experimental setting[1–13] but also in the intact heart.[14–16] Calculation of contractile indices is closely related to the underlying model and so they have been evaluated within the framework of the corresponding theories. In analogy to the mechanics of the isometrically contracting papillary muscle various shortening velocity indices have been derived for the determination of the intrinsic inotropic state in the intact heart.[14–17] Isovolumetric contractile indices have been used for the assessment of left ventricular contractility although several methodological limitations and assumptions have restricted their role in estimating contractile function in the clinical setting.[17–20] Calculation of isovolumetric contractile indices is dependent on the determination of the systolic stiffness index k. However, k was not determined in most clinical studies[17–20] because it is not possible to obtain an isovolumetric beat in the intact human heart. If however the relation of systolic stress rise between the isovolumetrically and the auxotonically contracting ventricle is known, the estimation of k and hence a meaningful determination of isovolumetric contractile indices becomes feasible. Thus as a first step we determined this relationship in seven patients with aortic valve disease under

Address for correspondence and reprints: Otto M Hess, MD, Medical Policlinic, Division of Cardiology, University Hospital, Raemistrasse 100, 8091 Zurich, Switzerland.

Key words: LV systolic function; series elasticity; myocardial structure; aortic valve replacement

Submitted 12 August 1987
Accepted 7 June 1988

normothermic conditions (37°C) during open heart surgery. In a second investigation we assessed systolic myocardial stiffness during cardiac catheterisation in 10 controls and 12 patients with severe aortic stenosis before and after aortic valve replacement, using the intraoperatively determined relation of stress rise between the isovolumetrically and the auxotonically contracting ventricle.

Methods

INTRAOPERATIVE MEASUREMENTS

In six patients with aortic stenosis (average mean systolic pressure gradient 66 mm Hg) and one patient with aortic regurgitation (regurgitant fraction 0.47) left ventricular short axis and left ventricular high fidelity pressure were measured simultaneously off bypass under normothermic conditions (37°C). Informed consent was obtained from all patients. After cannulation of the large vessels for cardiopulmonary bypass an 8F micromanometer angiocatheter was introduced into the left ventricle through the left atrial appendage. The catheter was fixed by a purse string (fig 1) and was left in place during the aortic valve replacement. The micromanometer pressure tracing was calibrated by matching it to the pressure obtained through the side lumen of the micromanometer. Two hemispheric ultrasonic piezo crystals[21] were sewn to the epicardium in the left ventricular equatorial axis (fig 1) and connected to a Triton 120 sonomicrometer. Bypass time was only minimally prolonged by the whole procedure and instrumentation took generally between 10 and 15 minutes. Calibration of the dimension gauges was carried out in 1 microsecond increments against a standard signal of precisely known duration derived from a stable crystal controlled oscillator (100 Hz). LV high fidelity pressure, LV epicardial short axis and the ECG were recorded simultaneously on an "Electronics for Medicine" VR 12 oscillograph at 250 mm·s^{-1} paper speed. Measurements were recorded before and after aortic valve replacement off bypass under normothermic conditions. Isovolumetric beats were produced by quick cross clamping of the ascending aorta for one or two consecutive beats (fig 2).

Data analysis — Left ventricular pressure and epicardial diameter tracings were digitised by hand with an electronic digitiser (Numonics Corp) interfaced to a DEC PDP 11/34 computer. The time interval of the data points was 10 milliseconds. All pressure and dimensional data were smoothed by an 11 point polynomial function.[22 23] The epicardial equatorial diameter of the left ventricle was measured continuously throughout the cardiac cycle. Endocardial chamber diameter and wall thickness were calculated because the ultrasonic crystals were placed epicardially to minimise myocardial injury and to keep the duration of the surgical intervention as short as possible. Left ventricular cross sectional muscle area (cm^2) was obtained from preoperative contrast ventriculography in the right anterior oblique

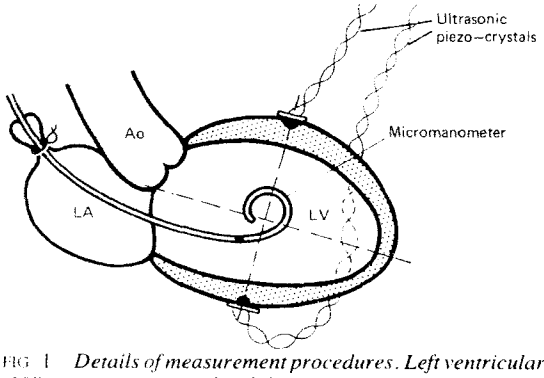

FIG 1 *Details of measurement procedures. Left ventricular (LV) pressure measured with 8F gauge Millar pigtail micromanometer catheter introduced through left atrial (LA) appendage. LV epicardial minor axis diameter measured simultaneously with two hemispherical ultrasonic crystals positioned on anterior and posterior LV wall.[21] Ao=ascending aorta.*

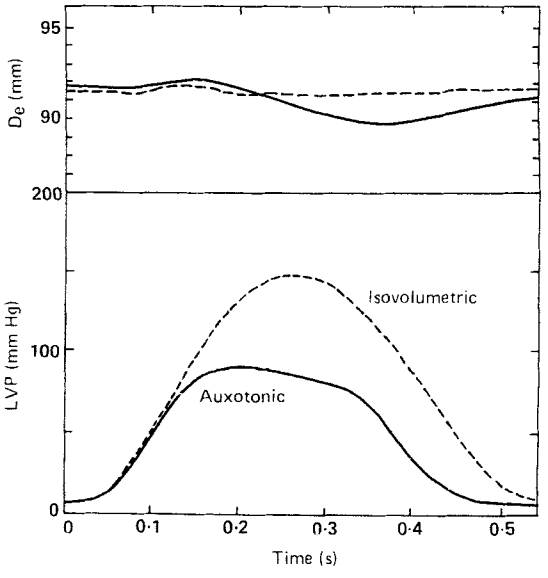

FIG 2 *Left ventricular epicardial minor axis diameter (D_e; upper panel) and left ventricular high fidelity pressure (LVP; lower panel) in normothermic patient with aortic valve disease during open heart surgery off bypass, showing superimposed auxotonic (solid line) and isovolumetric (dashed line) contractions. Peak systolic pressure is almost doubled with cross clamping of the ascending aorta, but maximal rate of LV pressure rise is unchanged. The epicardial minor axis diameter showed no shortening during aortic cross clamping.*

(RAO) projection at end diastole using the following equation:

$$CSA = \pi \left\{[(D_i + 2h_a)/2]^2 - (D_i/2)^2\right\},$$

where CSA = cross sectional muscle area (cm^2), D_i = LV angiographic end diastolic endocardial chamber diameter at the equator (cm), h_a = LV angiographic end diastolic wall thickness (cm).

A previous study using M-mode echo showed the CSA to change little over the first third of systole (2.4% difference between end diastole and peak systolic wall stress). We therefore assumed CSA to be constant over that period. We also assumed CSA to be the same intraoperatively and preoperatively. Intraoperative endocardial chamber diameter (D; cm) was then calculated from measured left ventricular epicardial diameter and angiographic cross sectional muscle area using the above equation reversed.

$$D = \sqrt{D_e^2 - 4\,CSA/\pi}$$

where D_e = sonographic LV epicardial diameter (cm). Instantaneous intraoperative wall thickness (h; cm) was calculated by subtracting D from D_e. Left ventricular meridional wall stress (S; $g \cdot cm^{-2}$) was determined using a cylindrical geometry for the left ventricular cavity as suggested by Brodie and coworkers[24] from simultaneous pressure-dimension data[25]

$$S = 1.36 \cdot [P \cdot D/4h(1+h/D)].$$

where P = LV high fidelity pressure (mm Hg).

The first time derivative of stress (dS/dt) was obtained by numeric differentiation of stress using a five point formula.[22] Left ventricular wall stress and dS/dt were determined at 10 ms intervals for one auxotonic beat and the consecutive isovolumetric beat obtained from aortic cross clamping (fig 2). According to Siegel and Sonnenblick,[26 27] dS/dt of the isovolumetric beat at peak stress of the auxotonic beat is approximately 90% of maximum dS/dt of the auxotonic beat in the experimental animal. In the present study we obtained a value of 87% for this relationship in the hypertrophied human left ventricle (fig 3; table 1a and b). This value was used in the intact human heart to calculate systolic myocardial stiffness.

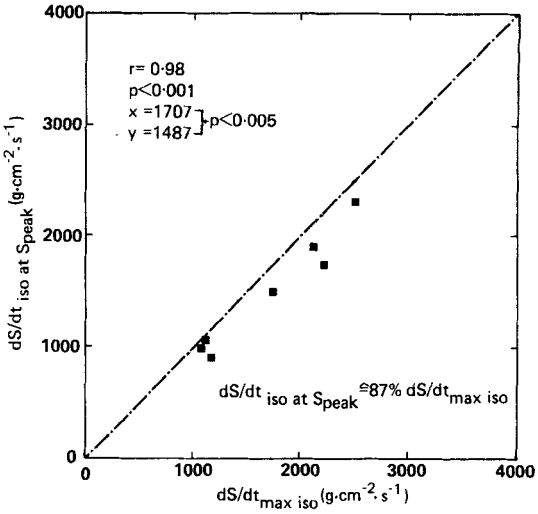

FIG 3 *Correlation between maximal rate of LV stress rise of the isovolumetric beat ($dS/dt_{max\ iso}$) and rate of LV stress rise of the isovolumetric beat at stress identical to auxotonic peak stress ($dS/dt_{iso\ at\ S\ peak}$) in 7 patients with aortic valve disease before (n=4) or immediately after (n=3, including the patient with aortic regurgitation) aortic valve replacement. Mean $dS/dt_{iso\ peak}$ was significantly ($p<0.005$) smaller (=87%) than $dS/dt_{max\ iso}$. Using this correlation we calculated dS/dt_{iso} at S peak by multiplying dS/dt_{max} of the auxotonic beat by 0.87 (for further explanations see text).*

TABLE 1 *Intraoperative data (n=7)*

(a) Measured data

	Auxo HR	*Iso HR*	*Auxo EDP*	*Iso EDP*	*Auxo LVSP*	*Iso LVSP*	*Auxo D_{ed}*	*Iso D_{ed}*
Mean	97	99	12	13	104	184*	7.35	7.33
SD	13	18	7	7	25	33	1.17	1.19

(b) Calculated data

	CSA	Auxo S_p	Iso Sp	Auxo max dS/dt	Iso max dS/dt	Iso dS/dt at Sp
Mean	21.0	148	255†	1547	1707	1487
SD	3.6	63	91	602	590	534

Auxo=data of the auxotonic beat; Iso=data of the isovolumic beat; HR=heart rate ($beats \cdot min^{-1}$); EDP=LV end diastolic pressure (mm Hg); LVSP=LV peak systolic pressure (mm Hg); D_{ed}=epicardial LV end diastolic diameter (cm). CSA=cross sectional muscle area (cm^2), derived from the preoperative RAO cineangiogram at end diastole; S_p=LV peak meridional stress ($g \cdot cm^{-2}$); max dS/dt=maximal rate of LV stress rise ($g \cdot cm^{-2} \cdot s^{-1}$); dS/dt at S_{peak}=maximal rate of LV isovolumic stress rise at auxotonic peak stress ($g \cdot cm^{2-1} \cdot s^{-1}$).
*greater than Auxo LVSP, $p<0.001$; †greater than Auxo Sp, $p<0.01$.

Determination of systolic myocardial stiffness — Systolic myocardial stiffness was calculated according to the technique of Forwand and coworkers[15]: it is assumed that at peak systolic stress of the auxotonic beat (dS/dt = 0) fibre shortening velocity is equal to the shortening velocity of the contractile element. In the isovolumetrically contracting heart this shortening velocity at peak stress is equal to the lengthening velocity of the series elastic element. These assumptions were used in the present study to calculate systolic myocardial stiffness index k ($circ^{-1}$), because k is an isovolumetric index and can otherwise only be determined by quick release methods.[14 28 29]

$$K=(dS/dl - c)/S,$$

where dS/dl is the stiffness of the series elastic elements and c is the intercept at zero stress; S is wall stress. It has been shown experimentally[29 30] that c is close to zero. Plotting dS/dl versus S in the present study (fig 4), it can be shown that stress intercept is also close to zero in the intact heart. Thus k was determined by the following simplified equation as proposed by Forwand and coworkers[15]:

$$k=0.87 \cdot (\max dS/dt/S_p \cdot Vcf_{atSp}),$$

where dS/dt is equal to maximal rate of stress rise and 0.87 is a constant, as determined from the intraoperative relation between dS/dt of the isovolumetrically and the auxotonically contracting ventricle (see above). S_p represents peak meridional systolic wall stress and Vcf normalised midwall circumferential fibre shortening velocity at peak stress ($circ \cdot s^{-1}$). Vcf was calculated from midwall circumference.[31]

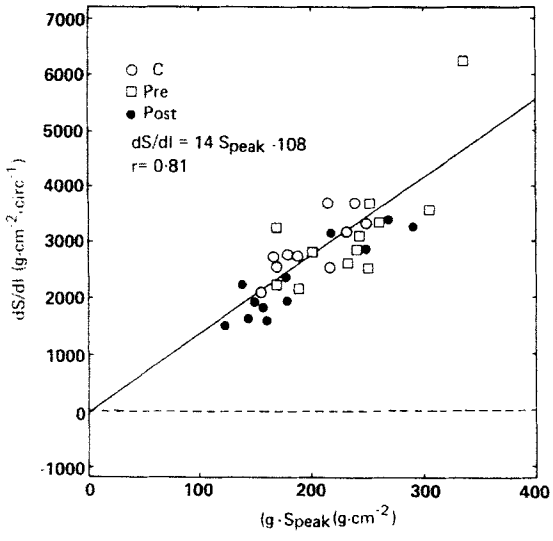

FIG 4 *LV peak stress (S_{peak}) — systolic stiffness relationship in 10 controls (C) and 12 patients with aortic stenosis before and after successful valve replacement. Since in individual patients only one data point was obtained and the slope of the stress-stiffness relationship could not be calculated, the intercept was assumed to be zero.*[12]

CATHETERISATION AND CINEANGIOGRAPHY

Ten patients with normal LV function, who underwent left heart catheterisation for atypical chest pain and had no or minimal heart disease, served as controls. Twelve patients with severe aortic stenosis (average mean systolic pressure gradient 72 mm Hg) and no or only slight aortic regurgitation (regurgitation fraction as determined by thermodilution <0.20) were examined pre- and postoperatively (mean postoperative follow up 19 months). After valve replacement there was a mild systolic pressure gradient (mean 9 mm Hg) in six patients. Selective coronary arteriography was carried out in all patients. Only one patient had minimal coronary artery disease with a <50% stenosis of the left anterior descending coronary artery. All patients were in sinus rhythm and the duration of the QRS complex did not exceed 0.11 s. Informed consent was obtained from all patients before catheterisation. Premedication consisted of 10 mg chlordiazepoxide (Librium^R) given orally 1 hour before the procedure. LV pressure was measured with a transseptally introduced 7F Millar micromanometer tipped angiographic catheter. The micromanometer was calibrated by superimposing the high fidelity pressure tracing on the conventional pressure tracing. Aortic pressure was measured through a fluid filled 8F gauge pigtail catheter. A peripheral lead of the standard electrocardiogram and the phonocardiogram were recorded, together with the high fidelity pressure measurements and the analogue dP/dt on an oscillograph "Electronics for Medicine" VR 12 at a paper speed of 250 $mm \cdot s^{-1}$. Biplane LV cineangiography was carried out in all patients in the right anterior oblique (30°) and left anterior oblique (60°) projections using 35 mm film at a filming rate of 50 frames per second. Each angiographic frame had a digital time which corresponded to the time marks on the pressure recordings.

Left ventricular endomyocardial biopsy — At the end of catheterisation, two or three left ventricular endomyocardial biopsies were taken transseptally from the anterolateral wall in patients with aortic stenosis, using a King's College bioptome introduced into the left ventricle through a 11.5 F gauge Brockenbrough catheter. Immediately after the biopsy was taken the material was fixed in glutaraldehyde and embedded in epon. Semithin sections of 1 μm were performed for light microscopy. Quantitative evaluation of left ventricular biopsies was carried out by morphometry.[32] Contraction bands and mechanical disruption of tissue architecture were occasionally seen and were excluded from analysis. Muscle fibre

diameter was determined from several cross sections at the level of the nucleus with a mechanical optical pen (Kontron GmbH, Zurich). At least 100 measurements were obtained with this pen from each biopsy specimen and the average fibre diameter with standard deviation was calculated. Interobserver variability was found to be 1.3% in 22 patients. Interstitial non-muscular tissue was evaluated by a point counting system. A special eye piece with a grid providing 100 intersection points was used to determine the interstitial non-muscular tissue. The predominant component of the interstitial space is fibrous tissue and therefore the term "interstitial fibrosis" was also used to describe the interstitial non-muscular tissue. Usually 1000 intersection points were counted with this grid and the average interstitial non-muscular tissue, with standard deviation, was calculated in each biopsy. Interobserver variability was found to be 6.2% for determination of interstitial non-muscular tissue in 18 patients.

Data analysis — Biplane angiographic and simultaneous high fidelity pressure data were usually obtained for one representative beat providing adequate opacification during contrast medium injection. Extrasystolic and postextrasystolic beats were excluded from the analysis. Biplane left ventricular volumes were determined frame by frame according to the "area-length" method.[33] From the biplane angiograms chamber diameter was determined and the geometric mean of the left and right anterior oblique projections was calculated. All dimensional data were smoothed using a 5 point polynomial equation.[31] Left ventricular end diastolic wall tickness (cm) and muscle mass (g) were determined according to the technique of Rackley *et al.*[34] Instantaneous wall thickness was calculated throughout the cardiac cycle as described originally by Hugenholtz and coworkers.[35] Fibrous content was calculated from interstitial fibrosis (IF) and left ventricular muscle mass (LMM): IF·LMM/100 ($g \cdot m^{-2}$). Left ventricular pressure tracings were digitised manually with an electronic digitiser (Numonics Corp.) interfaced to a DEC PDP 11/34 computer. End diastole was defined as the cineangiographic frame occurring immediately prior to the rapid upstroke of the simultaneously recorded analogue dP/dt. End systole was defined as the frame which coincides with a left ventricular pressure identical to the incisural pressure on the aortic pressure tracing.

STATISTICS

Statistical analysis between controls and patients with aortic stenosis pre- and postoperatively was performed by a one way analysis of variance. If the analysis was significant, the Scheffe procedure was applied. Pre- and postoperative comparisons were carried out by a paired Student *t* test. In all tables and figures the means(SD) are given.

Results

A representative auxotonic and isovolumetric contraction in a patient with severe aortic stenosis is illustrated in fig 2 during open heart surgery off bypass under normothermic conditions.

INTRAOPERATIVE DATA (tables 1a and 1b)

Heart rate, left ventricular end diastolic pressure and end diastolic epicardial diameter (table 1a) were not significantly different between the auxotonic and the isovolumetric beat. However, peak systolic pressure increased significantly from 104 to 184 mm Hg during aortic cross clamping. The calculated end diastolic endocardial chamber diameter and end diastolic wall thickness remained unchanged before and after aortic cross clamping. Peak systolic meridional wall stress increased significantly from 148 to 255 $g \cdot cm^{-2}$ during aortic cross clamping, whereas the maximal rate of systolic wall stress increase (max dS/dt) increased slightly although not significantly after cross clamping (table 1b). This confirms that contractility from rest to cross clamping remained unchanged.

CARDIAC CATHETERISATION (tables 2 – 5)

Standard haemodynamics (table 2) — Heart rate, max dP/dt and left ventricular ejection fraction were not significantly different between controls and patients with aortic stenosis before and after aortic valve replacement. Left ventricular end diastolic and peak systolic pressure, left ventricular end diastolic

TABLE 2 *Standard haemodynamics. Results are means(SD)*

	HR	*LVEDP*	*LVSP*	*max dP/dt*	*EF*	*EDVI*	*LMMI*
Controls (n=10)	69(12)	11(3)	130(18)	1601(355)	63(3)	88(17)	87(9)
AS pre-op (n=12)	79(11)	27(11)‡	225(33)‡	1810(331)*	56(12)	123(29)*	191(46)‡
AS post-op (n=12)	73(12)	24(9)†	163(18)¶	1600(247)	60(10)	107(23)	145(39)§†

HR=heart rate ($beats \cdot min^{-1}$); LVEDP=LV end diastolic pressure (mm Hg); LVSP=LV peak systolic pressure (mm Hg); max dP/dt=maximal rate of LV pressure rise ($mm\,Hg \cdot s^{-1}$); EF=LV biplane ejection fraction (%); EDVI=Lv end diastolic volume index ($ml \cdot m^{-2}$); LMMI=LV muscle mass index ($g \cdot m^{-2}$); AS pre-op=preoperative aortic stenosis; AS post-op=postoperative aortic stenosis.
*$p<0.05$ *v* controls; †$p<0.01$ *v* controls; ‡$p<0.001$ *v* controls; ¶$p<0.001$ *v* pre-op; §$p<0.01$ *v* pre-op.

TABLE 3 *Systolic myocardial stiffness. Results are means(SD).*

	S_{peak}	max dS/dt	Vcf at S_{peak}	k
Controls (n=10)	199(34)	2998(555)	0.91(0.16)	15(1)
AS pre-op (n=12)	239(51)	2394(666)	0.69(0.18)*	14(3)
AS post-op (n=12)	188(55)†	2471(828)	0.97(0.20)‡	12(2)*

S_{peak}=LV peak systolic meridional wall stress ($g \cdot cm^{-2}$); max dS/dt=maximal rate of LV systolic stress rise ($g \cdot cm^{-2} \cdot s^{-1}$); Vcf at S_{peak}=instantaneous midwall circumferential fibre shortening velocity at peak stress ($circ \cdot s^{-1}$); k=systolic myocardial stiffness index ($circ^{-1}$); AS pre-op=preoperative aortic senosis; AS post-op=postoperative aortic stenosis.
*p<0.01 *v* controls; †p<0.05 *v* pre-op; ‡p<0.01 *v* pre-op.

TABLE 4 *Microscopic structure in pre- and postoperative aortic stenosis. Results are means(SD).*

	MFD	IF	FC
AS pre-op (n=12)	31.8(4.6)	15.4(5.2)	29.7(13.3)
AS post-op (n=12)	27.2(3.6)†	26.2(9.8)*	37.9(19.2)

MFD=muscle fibre diameter (μm); IF=interstitial fibrosis (%); FC=fibrous content ($g \cdot m^{-2}$); AS pre-op=preoperative aortic stenosis; AS post-op=postoperative aortic stenosis.
*p<0.05 *v* pre-op; †p<0.01 *v* pre-op.

TABLE 5 *Correlations between systolic stiffness index k, and macroscopic and microscopic structure*

			n	r	p
k	*v*	EF	24	–0.40	NS
k	*v*	EDVI	24	0.40	NS
k	*v*	LMMI	24	0.38	NS
k	*v*	MFD	24	0.55	<0.01
k	*v*	IF	24	–0.31	NS
k	*v*	FC	24	–0.09	NS
dk	*v*	dEF	12	–0.19	NS
dk	*v*	dEDVI	12	0.23	NS
dk	*v*	dLMMI	12	0.36	NS
dk	*v*	dMFD	12	0.66	<0.02
dk	*v*	dIF	12	–0.37	NS
dk	*v*	dFC	12	–0.29	NS

k=systolic stiffness index ($circ^{-1}$); EF=LV systolic ejection fraction (%); EDVI=LV end diastolic volume ($ml \cdot m^{-2}$); LMMI=LV muscle mass ($g \cdot m^{-2}$); MFD=muscle fibre diameter (μm); IF=interstitial fibrosis (%); FC=fibrous content ($g \cdot m^{-2}$).

volume and muscle mass were significantly increased in preoperative patients with aortic stenosis compared to controls. Following successful valve replacement there was a significant decrease in left ventricular peak systolic pressure and left ventricular muscle mass. However, left ventricular end diastolic and peak systolic pressure, as well as left ventricular muscle mass, remained significantly elevated following valve replacement when compared to controls.

Systolic myocardial stiffness (table 3) — Left ventricular peak systolic wall stress was slightly but not significantly elevated in preoperative patients with aortic stenosis. After aortic valve replacement peak systolic wall stress decreased significantly in patients with aortic stenosis. Max dS/dt was similar in all three groups, whereas circumferential fibre shortening velocity at peak systolic wall stress was significantly decreased in preoperative patients with aortic stenosis but became normal after successful valve replacement. Systolic myocardial stiffness index k was preoperatively normal in patients with aortic stenosis but decreased significantly after valve replacement when compared to controls. Since the intercept of the load-stiffness relationship (fig 4) cannot be determined in the intact human heart, we plotted dS/dl versus peak stress in all patients and observed a good correlation (r = 0.81) with an intercept close to zero.

Microscopic structure in pre- and postoperative aortic stenosis (table 4) — Quantitative analysis of endomyocardial biopsy samples showed preoperatively an increase in muscle fibre diameter (normal <20 μm). Following surgery muscle fibre diameter decreased significantly from 31.8 to 27.2 μm ($p<0.01$). Interstitial fibrosis showed a significant increase from 15.4 to 26.2% ($p<0.05$) after aortic valve replacement. Fibrous content remained unchanged before and after valve replacement.

Correlations between systolic myocardial stiffness, left ventricular function and microscopic structure (table 5) — The relationship between systolic stiffness and LV function (ejection fraction, end diastolic volume index and left ventricular muscle mass index) was evaluated in patients with aortic stenosis. There was no significant correlation between these variables or between their pre- and postoperative differences. The relationship between systolic stiffness and myocardial structure showed a significant correlation for myocardial stiffness versus muscle fibre diameter and for the pre-/postoperative difference of systolic stiffness versus that of muscle fibre diameter. There were no correlations with the degree of interstitial fibrosis or with the fibrous content.

Discussion

Systolic myocardial stiffness of the intact left ventricle has been evaluated in the experimental animal,[15] in

patients with normal left ventricular function and in patients with dilated cardiomyopathy.[16] Since in the intact human heart it is not possible to obtain an isovolumetric beat for calculation of the systolic myocardial stiffness index k, several assumptions have to be made for its calculation. Most authors have used a stiffness index of 28 muscle lengths^{-1}, which has been derived from the cat papillary muscle.[10 11 28 29] Besse and coworkers[16] calculated the systolic stiffness index assuming that the rate of systolic stress rise at peak stress of the auxotonic beat is 90% of maximal dS/dt of the isovolumetric beat. This assumption was made on the basis of the work of Siegel and Sonnenblick.[26 27] Because no such data are available in man, we assessed in the first part of our study the relationship between the isovolumetrically and auxotonically contracting left ventricle in patients with aortic valve disease during open heart surgery. In the second part, overall systolic myocardial stiffness of the left ventricle was determined during catheterisation in 10 controls and 12 patients with chronic pressure overload before and after valve replacement, using the intraoperatively determined relationship.

FACTORS WHICH AFFECT SYSTOLIC STIFFNESS

Preoperative patients with aortic stenosis showed a similar k value when compared to controls, despite markedly increased angiographic mass. After successful valve replacement k was significantly lower in aortic stenosis than in controls, suggesting a decrease in overall systolic stiffness. In the present study the systolic stiffness index k was considerably lower than in the previously published experimental[10] and clinical[16] studies. This can be attributed to the fact that systolic stiffness is affected in the intact heart by factors other than series elasticity of the myocardium itself, including the non-homogeneity of myocardial structure, electrical activation and ventricular geometry of the heart muscle. Another factor is the difference in temperature between the experimental[10] and the clinical studies.[16] According to Templeton and coworkers,[30] an increase in temperature from 22° to 37°C is accompanied by a decrease in myocardial stiffness of 20-30%. Thus our observation that systolic stiffness is approximately 15 circ^{-1} in the intact heart seems to be reasonable compared to experimental data[13 14] from the cat papillary muscle.

EFFECT OF MORPHOLOGY ON SYSTOLIC STIFFNESS

Series elastic properties are most likely to be related to the contractile element itself rather than to the connective tissue of the myocardium.[29] Therefore systolic stiffness index k was correlated to left ventricular function and myocardial structure in patients with aortic stenosis (table 5). There was no correlation between systolic stiffness index k and angiographic variables. With respect to the morphometric variables, k was only correlated to muscle fibre diameter, suggesting that series elasticity is determined by structures related to the heart muscle cell itself and not to the surrounding connective tissue. Hence a functional defect of the muscle cell independent of its shortening capacity[29] appears to be responsible for the decrease in systolic stiffness after aortic valve replacement. A similar decrease in systolic stiffness was observed in the experimental animal following chronic myocardial infarction.[15] It was suggested that the decrease in systolic stiffness was due to structural alterations of the myocardium. However, myocardial infarction is associated with regional differences in structure and function and therefore global function measures only partly characterise systolic myocardial stiffness. In contrast, aortic valve disease is accompanied by more or less diffuse changes of the left ventricular myocardium. Although there might be structural differences from the subendo- to the subepicardium, determination of an overall systolic stiffness parameter appears to be appropriate.

LIMITATIONS OF THE STUDY

Derivation of contractile indices is based upon the muscle model used; the analysis and the results are, therefore, strongly dependent on the underlying theoretical concept. The two component model of Hill was first developed in skeletal muscle and has been transferred to cat papillary muscle in the early sixties. Despite the restrictions inherent in this model it remained the most frequent approach applied in assessing contractile function until now.

Whether meridionial wall stress is representative of left ventricular myocardial load could be debated. In a previous study[25] we have, however, shown excellent correlations between meridionial wall stress and other wall stresses, calculated on the basis of a more complex ventricular geometry. In five different stress models qualitatively the same results were obtained with respect to end diastolic and mean systolic stress (unpublished data). One basic problem for the assessment of systolic myocardial stiffness in the intact heart is related to the impossibility of obtaining an isovolumetric beat for calculation of the rate of stress rise at peak systolic stress of the auxotonic beat. To solve this problem we determined the relation between the rate of stress rise (dS/dt) of the isovolumetric beat at peak stress of the auxotonic beat and the maximal rate of stress rise (max dS/dt) during open heart surgery in seven patients with aortic valve disease. This has not been done before in humans but nicely confirms the results obtained from experimental studies by Siegel and Sonnenblick.[26 27]. The mean

value of this relationship in our study was 0.87. The minimum value in our seven intraoperative patients was 0.77, the maximum value 0.95. Thus small variations in systolic stiffness index might be due to some variation in the relationship between isovolumetric dS/dt at peak auxotonic stress and maximum dS/dt. Since wall thickness could not be measured during surgery, it was calculated from the sonographic epicardial minor axis diameter, assuming a constant cross sectional muscle area which was determined from preoperative angiocardiography. This assumption might lead to a certain overestimation of calculated left ventricular endocardial short axis and hence of calculated wall stress with increasing LV shortening, due to an eventual increase in cross sectional muscle area resulting from long axis shortening. However, the increase in echocardiographic cross sectional muscle area in 10 patients with aortic stenosis was only minimal (+2.4%) from end diastole to peak systolic wall stress.

CLINICAL IMPLICATIONS

The isovolumetric contractile indices have been shown to be of minor importance for the assessment of contractility in man[19] due mainly to their low sensitivity for detecting abnormal or reduced left ventricular function. Nevertheless the systolic stiffness index reflects one of the important material constants of the myocardium which is related to the properties of the series elastic elements. Alterations of series elasticity might not be reflected by structural alterations of the myocardium with augmented connective tissue, but might be represented by a qualitative change of the heart muscle cells. Although the ejection phase variables such as systolic ejection fraction or mean circumferential fibre shortening velocity might be more sensitive in detecting left ventricular dysfunction,[19] the systolic stiffness index and therefore the isovolumetric contractile indices provide important information on the contractile state of the left ventricle.

In the present study the systolic stiffness index k decreased in patients with aortic stenosis following successful valve replacement (table 3), whereas systolic ejection performance remained normal before and after valve replacement (table 2). Apparently, the systolic stiffness index reflects a reduction in series elastic properties of the left ventricle after aortic valve replacement. In this situation the stiffness index might help to differentiate between a ventricle with normal or abnormal series elasticity in the presence of a normal ejection performance.

CONCLUSIONS

Systolic myocardial stiffness index was found to be about 50% smaller than the generally accepted value in the literature, which is derived from cat papillary muscle. As shown by Templeton and coworkers[30] the temperature effect and the intrinsic difference in systolic stiffness of the isolated papillary muscle and the intact heart probably explain the decrease in systolic stiffness found in our study compared to previous experimental studies. Systolic myocardial stiffness was normal in preoperative patients with aortic stenosis but decreased following successful valve replacement. The postoperative decrease in systolic stiffness index suggests a functional defect of series elastic properties which is not related to the interstitial fibrous tissue but to alterations of the heart muscle cell itself, independent of the shortening capability of the left ventricle.

Supported by a grant from the Swiss National Science Foundation.

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